PERSPECTIVE

A reference standard for the measurement of macular oedema

K A Goatman

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Macular oedema is associated with several conditions that lead to blindness. Accurate measurement of macular thickness is important in order to follow disease progression and evaluate treatments. Four techniques are examined to determine the best reference standard for the detection and quantification of macular oedema: ultrasound, optical coherence tomography, the retinal thickness analyser, and the scanning laser ophthalmoscope. The three optical techniques have the highest resolution and sensitivity, in particular optical coherence tomography. Ultrasound can be useful where dense opacities preclude optical imaging.

Macular oedema is associated with several conditions that cause irreversible vision loss.[1] These include diabetic retinopathy,[2] uveitis,[3] venous occlusion,[4] and trauma—for instance, following cataract surgery.[5]

Macular oedema may be classified according to the fluid distribution: diffuse oedema is a general thickening caused by extensive capillary dilation, while focal oedema is centred on specific vascular abnormalities, such as microaneurysms. Accumulated fluid defocuses the image on the retina, reducing visual acuity. If oedema persists it may lead to irreparable photoreceptor damage.[1]

Macular oedema has traditionally been assessed clinically using a combination of slit lamp biomicroscopy, stereo photography and stereo fluorescein angiography. However, these techniques have a number of limitations. Foremost is that they are only qualitative assessments, which are relatively insensitive to thickness changes.[6] Furthermore, slit lamp examination does not provide a pictorial record and, together with stereo photography, is known to be biased by the presence or absence of exudates.[7] Although the stereo angiogram is a sensitive test for leakage, the assessment of thickening is very subjective. Best corrected visual acuity has also been used as a surrogate indication of thickening, but is neither sensitive nor specific, being affected by several factors besides macular thickness.[8]

Objective, quantitative measures of macular thickening are important both in research and in clinical practice. They facilitate the measurement of disease progression and treatment efficacy. Four techniques, based on different imaging technologies, are reviewed here: ultrasound, optical coherence tomography (OCT), the retinal thickness analyser (RTA), and the Heidelberg retinal tomograph (HRT) confocal scanning laser ophthalmoscope. Table 1 compares the resolutions of the four techniques in both the axial (perpendicular to the retinal surface) and lateral (parallel to the retinal surface) directions. However, resolution is not the only consideration; on the technical side, contrast, repeatability and reproducibility are equally important and, from the practical point of view, patient comfort will determine compliance, especially in longitudinal studies.

ULTRASOUND

The fluid filled structure of the eye is ideal for ultrasound examination, and the eye was one of the first medical applications of ultrasound.[9]

The principle of ultrasound

For retinal imaging, ultrasound frequencies between 10 MHz and 20 MHz are the most useful. Higher frequencies result in greater resolution, but at the expense of penetration; frequencies as high as 50 MHz have been used to view the anterior segment, but do not have sufficient penetration to image the retina.

An A-scan is a single axial profile, recording the strength of echoes from different depths. Interfaces between materials with different acoustic impedances generate strong echoes, while materials that scatter ultrasound return more diffuse echoes. Fluid filled structures, such as the vitreous or cysts, neither reflect nor scatter ultrasound significantly. There is, therefore, good contrast between fluid filled oedema and normal retinal tissue. A two dimensional axial cross section, known as a B-mode image, is generated from multiple A-scan lines. Three dimensional ultrasound imaging, popularly used for fetal imaging, has been used to measure choroidal melanoma volume.[10] However, the resolution is currently too poor to measure macular oedema volume accurately.

Although ultrasound examination cannot compete with the resolution of OCT, it has a role where optical opacities, such as cataract or vitreous haemorrhage, prevent optical imaging.

Correspondence to:
Dr Keith A Goatman,
Department of Radiology,
University of Aberdeen,
Foresterhill, Aberdeen
AB25 2ZD, UK;
k.a.goatman@abdn.ac.uk

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Abbreviations: COV, coefficient of variation; FA, fluorescein angiography; HRT, Heidelberg retinal tomograph; OCT, optical coherence tomography; RPE, retinal pigmentation epithelium; RTA, retinal thickness analyser; SLO, scanning laser ophthalmoscope

Table 1 Resolution comparison of the techniques reviewed

Method	Axial resolution (μm)	Lateral resolution (μm)
Ultrasound (B-mode)	150–200	200–500
Optical coherence tomography (cross section)	2–15	10–20
Optical coherence tomography (thickness map)	2–15	10 (centre) to 1500 (edge)
Heidelberg retinal tomograph	150–300	10–20
Retinal thickness analyser	50	380

The performance of ultrasound

Resolution

The most commonly used probes operate at 10 MHz, with an axial resolution of 150–200 μm and a lateral resolution of approximately 250–500 μm, although higher resolution 20 MHz probes are becoming more common.[11 12] There is no advantage in using transducers above 25 MHz.[13]

Sensitivity

Few studies have evaluated macular thickness measurement using ultrasound. However, Lai and colleagues, comparing ultrasound with a gold standard of slit lamp, fluorescein angiography (FA), and OCT, found the sensitivity and specificity of ultrasound to be 91% and 96%, respectively.[14]

Repeatability and reproducibility

The operator dependent orientation of cross sections can make retrospective interpretation and repeat measurements difficult. Three dimensional imaging may help in this regard, provided that the resolution improves.

OPTICAL COHERENCE TOMOGRAPHY

The introduction of OCT improved the axial resolution of retinal cross sections, formerly only possible using ultrasound, by two orders of magnitude. OCT has since become popular as a rapid, non-invasive technique ideal for longitudinal studies.[15 16]

The first commercial system, designated OCT1 here, was launched in 1996 by Carl Zeiss Meditec (http://www.meditec.zeiss.com). The latest system, named Stratus OCT and here referred to as OCT3, was released in 2001. It includes many improvements over the earlier OCT1 and OCT2 systems, such as higher axial and lateral resolution, better signal to noise ratio and faster acquisition.

The principle of OCT

A number of reviews have covered the technology and ophthalmic applications of OCT.[4 17–20] It is based on low coherence interferometry, and was first demonstrated in biological tissues in the early 1990s.[21] Commercial systems use super-luminescent diode lasers as the light source, whereas ultrahigh resolution research systems use more expensive titanium:sapphire lasers.[22–24] Both laser types are centred on infrared wavelengths. Measurements are made by splitting the light beam: one part directed to the retina and the other to a moving reference mirror. When the distance between the source and the reference mirror is equal to the path length of light from the retina, an interference pattern is produced on a Michelson interferometer. A depth profile, analogous to the ultrasound A-scan, is created by recording the magnitude of the interference pattern for different path lengths. In OCT3, each A-scan line consists of 1024 measurements over a 2 mm depth range.

A second mirror linearly translates the beam to generate a cross section of multiple A-scan lines analogous to the ultrasound B-mode image. OCT3 can acquire B-mode images with 128, 256, or 512 A-scan lines at a rate of 400 lines per second. This is an improvement on the OCT2 system, which only acquired 100 lines per second.

Two dimensional thickness maps, where the colour indicates the thickness of a particular area, may be generated by automatically detecting the retinal boundaries in the cross sectional images. However, OCT acquisition, even using OCT3, is relatively slow, which limits the resolution of the thickness map. The current protocol is based on six intersecting radial cross sections.[25] This results in very poor resolution away from the intersecting spokes, which is seen as radial smearing. Experimental systems based on Fourier domain, rather than time domain, techniques acquire cross sections faster. For instance, Schmidt-Edfurth and colleagues have demonstrated a system capable of 25 cross sections per second.[24]

While earlier systems required at least a 5 mm pupil, OCT3 requires only a 3 mm pupil which, coupled with the infrared illumination, means that mydriasis is not always necessary.[26 27] Ocular refractive errors affect lateral, but not thickness, measurements.

What does OCT actually show?

OCT records light reflected from interfaces between materials with different refractive indices, and from materials that scatter light. Everything else is invisible to OCT, regardless of the device resolution.

While OCT clearly provides unprecedented clarity and definition of retinal structures in vivo, debate has raged concerning which anatomical structures correspond to specific OCT features. Several studies have demonstrated a clear and predictable relation between OCT and histology.[28–31] Chauhan and Marshall reported that the bright band corresponding to the nerve fibre layer was more than seven times wider than that found by histology, and that the band persisted despite considerable laser ablation.[32] However, this is not surprising given the OCT1 instrument resolution, and there is no reason that the bright interface should be specific to the nerve fibre layer; it simply indicates a step change in refractive index between the layers, in this case between the vitreous and what remained of the retina.

OCT1 systems resolve two highly reflecting layers, which were originally assumed to correspond to the vitreous/retina and retinal pigment epithelium (RPE)/choriocapillaris interfaces. Commercial software was developed to measure the distance between these two layers, which was taken to be the retinal thickness. However, OCT3 is able to resolve three highly reflecting layers,[33] believed to correspond to the vitreous/retina, inner/outer photoreceptor segments, and RPE/choriocapillaris interfaces. Ultrahigh resolution systems are able to resolve a fourth layer, possibly the external limiting membrane.[34] Correct identification of these features is vital if retinal thickness is to be measured accurately.

The performance of OCT

Resolution

The axial resolution of commercial OCT systems is approximately 8–16 μm. The lateral resolution is between 10 μm and 15 μm, comparable to a fundus camera. The resolution of

thickness measurements depends as much on the software as the hardware, in particular the accuracy and precision with which the retinal boundaries are detected.

Ultrahigh resolution systems have axial resolutions of the order of 2–3 μm. Ko *et al* compared an ultrahigh resolution system with OCT3.[35 36] However, it is unlikely that resolution can be improved much further because of optical aberrations in the eye.

Sensitivity

Several investigators have compared OCT with slit lamp biomicroscope examination, concluding that OCT is the more sensitive test for thickening.[6 7 37–42] Indeed, OCT is even able to measure circadian variation in diabetic retinal oedema.[43] Hee *et al* found slit lamp and OCT agreement was good for normal and extreme thicknesses, but equivocal between 200 μm and 325 μm.[25] Strøm *et al* found good agreement between thickening seen on stereo photographs and OCT.[44] Studies comparing OCT and FA indicate OCT to be at least as sensitive as angiography for detecting thickening.[42 45 46]

Repeatability and reproducibility

Muscat *et al* assessed accuracy, precision, repeatability, and reproducibility of OCT1 measurements using a test object and 20 normal controls.[47] The test object results showed that OCT produces accurate and precise measurements that are repeatable and reproducible. Similarly, the results from the control subjects were repeatable and reproducible, with an inter-session reproducibility of 1.5%. Other groups have measured similar values for normal subjects: 1.4–2.4%,[8] 1.2%,[26] 3.2–8.1%,[48] and 7.2%.[25]

Direct comparison of reproducibility studies is difficult; experimental and statistical methods vary between studies. Nevertheless, the clear consensus is that OCT macular thickness measurements are highly reproducible and repeatable. Reasons for study differences include:

- *Region position:* Measurements taken at or near the fovea are subject to greater variation than elsewhere, because of the rapid change in thickness at the fovea. Longer acquisition times exacerbate the problem, allowing more time for fixation to drift.
- *Region size:* Measurements made over larger areas are less susceptible to small positional errors. Similarly, volume measurements tend to be more reproducible, although less sensitive to genuine change, than thickness measurements.[49]
- *Retinal health:* Measurements made of healthy retinas, free from attenuating oedema and lesion artefacts, are more reproducible.[50] An early study investigating the reproducibility of central foveal thickness (measured as the standard deviation of the centre values of the six radial lines) found it to be 11 (6) μm (mean (SD)) in normal eyes, and 20 (11) μm in eyes with visible retinopathy.[25] A recent OCT3 study similarly measured the reproducibility to be 11 μm in normal eyes.[51] Dense cataracts and vitreous opacities may prevent acquisition of an acceptable image, although OCT has been shown to be more effective than the slit lamp or RTA in these situations.[44 50 52]
- *OCT model:* Improvements in the hardware and software of the latest OCT system have resulted in a much lower incidence of artefacts in the presence of oedema. However, thickness measurements made using OCT3 appear to be significantly higher, by an average 8.1%, than with OCT1, an important consideration for multicentre and longitudinal studies.[53] Similarly, Chan *et al* found the mean normal thickness using OCT3 to be 38–62 μm thicker than that reported using earlier equipment.[51] Paunescu *et al*,[54] investigating macular thickness reproducibility using OCT3, compared their results with those of Massin *et al*,[55] using OCT2. They suggest that the superior reproducibility they report is the result of technological improvements. However, the cohort used by Paunescu consisted only of healthy subjects, while Massin's included eyes with clinically significant macular oedema. When the patients with clinically significant macular oedema are excluded, the reproducibilities are comparable.
- *Equipment settings:* OCT3 has many adjustable acquisition parameters. For instance, resolution can be traded for acquisition time. When acquiring a thickness map there is the option of a fast or a regular map. Both collect data along six intersecting radial spokes, which may be either 3.4 mm or 6 mm in length. The fast map option acquires 128 A-scans in each spoke, and the regular map 512 lines. The fast scan acquires all six lines automatically in 1.9 seconds, whereas the lines are acquired separately for the regular map. Faster acquisition reduces the likelihood of eye movement during scanning. Studies have shown the fast map to be reproducible,[27] and comparable with the regular protocol.[54 56 57]
- *Manual or automated analysis:* Software is provided to measure thickness automatically. However, there has been uncertainty concerning which OCT features represent the retinal boundary. A number of authors concluded that the errors in the automated measurements were too large in practice.[7 58] In contrast, Koozekanani *et al*[26] found no significant difference between manual and automatic thickness measurements, but the study only included 26 normal eyes. Measurement errors are less frequent in macular oedema than for macular holes and choroidal neovascularisation.[57 58]
- *Operator experience:* Ray and colleagues found that incorrect boundary identification and poor image quality were the two most common reasons for errors using fast retinal maps. Since an error in any of the six radial scans may affect the resulting map, artefacts are much more likely in the thickness map than single cross sections: errors in at least one radial line were noticed in 43% of maps, which affected 27% of the central thickness measurements.[50] However, Hee suggests that most of these artefacts can be eliminated by improved operator training and careful acquisition.[59]
- *Mydriasis:* Unlike nerve fibre layer and optic nerve head measurements,[54] mydriasis appears to have no significant effect on the reproducibility of macular thickness measurements.[27]

RETINAL THICKNESS ANALYSER

The retinal thickness analyser was launched in 2000 by Talia (Talia Technology Ltd, Israel; http://www.talia.com), based on research from Johns Hopkins University.[60] It includes an integrated fundus camera and laser based thickness measurement system.

The principle of the RTA

The RTA is a non-contact device that makes thickness measurements based on the same principle as the slit lamp biomicroscope. A green (543 nm) helium-neon laser is projected as a slit, 3 mm long and approximately 15 μm wide, obliquely onto the retina. Since the beam is not perpendicular to the surface, reflections from different depths appear translated laterally; for the 15° angle used, every 100 μm increase in depth results in a 27 μm lateral translation. Hence, the lateral separation between the reflections from the vitreoretinal and chorioretinal interfaces gives a measure of retinal thickness. The green wavelength provides good contrast for the retinal interfaces. However, the

eye is very sensitive at this wavelength and, since at least a minimum 4 mm pupil is required, mydriasis is essential.

The slit reflection is recorded using a CCD camera. Software divides the line into 16 segments, and estimates the thickness of each by fitting a curve to the intensity distribution. The distance between the peaks is assumed to be the retinal thickness. The laser slit is stepped across the retina to create a thickness map.[61] The current system acquires 16 slit images 188 μm apart, covering a 3×3 mm region of the retina in 300 ms. The standard protocol acquires five such regions: four in a 2×2 non-overlapping square grid covering a 6×6 mm area, and an additional overlapping region centred on the fixation point.

The performance of the RTA

Resolution

Zeimer *et al* measured the axial resolution to be 50 μm.[60] This is for eyes with clear media; several authors comment on the adverse effect even minor opacities have on resolution.[62–67] Ocular refractive errors affect thickness measurements.

Sensitivity

Neubauer *et al* compared the RTA with clinical examination (slit lamp biomicroscopy and, if requested, fluorescein angiography) for a consecutive series of 31 eyes.[68] The sensitivity for macular oedema detection was 100% and the specificity ranged from 58% to 96%, depending on the grader. RTA assessment failed for one eye because of poor image quality.

Pires *et al* compared the RTA and OCT with seven field stereo photography.[69] None of the photographs were graded as having clinically significant macular oedema. Nevertheless, significant thickening was reported in 86% (24/28) of eyes using the RTA, and in 11% (3/28) using OCT. The authors attribute this difference to the superior sensitivity of the RTA. However, Goebel *et al* found OCT to be more sensitive than the RTA,[67] suggesting that the earlier result may be the result of oversensitivity or poor specificity. One possibility is that an inappropriate normative database was used—several studies have shown that retinal thickness is significantly greater in people with diabetes, even with no sign of retinopathy, than in normal controls.[7] Two other studies have reported poor agreement between the RTA and stereo photography. Yang *et al*, treating the RTA result as the gold standard, found the sensitivity and specificity of the stereo photographs to be 79% and 58%, respectively.[64] In contrast with an earlier study, which found good agreement between OCT and stereo photography,[44] Strøm *et al* found poor agreement between the RTA and stereo photography.[44]

Repeatability and reproducibility

Polito *et al* found automated RTA measurements were successful in only 49% (27/55) of eyes, compared with 98% (54/55) of eyes using OCT.[63] Reasons for failure included ocular media abnormalities, scarring, and excessive intra-retinal fluid near the retinal edge. Goebel *et al* found the RTA to be more prone to errors than OCT in diabetic retinas.[67] Weinberger *et al* measured the RTA intra-session repeatability to be plus or minus 5.9% (plus or minus 10.6 μm), and the inter-session reproducibility to be plus or minus 6.6% (plus or minus 10.8 μm) in a study including both normal and diabetic retinas.[70] Gilmore *et al* measured the intra-session coefficient of variation (COV) to be 11% at the fovea and 3.5% to 5.0% elsewhere,[71] similar to the variation seen using OCT.

SCANNING LASER OPHTHALMOSCOPE

The scanning laser ophthalmoscope was first demonstrated by Webb *et al*.[72] Laser scanning brought several advantages over the traditional fundus camera. Firstly, it is more efficient; the average illumination power is two orders of magnitude lower than the fundus camera since only a single spot is illuminated at one time. Secondly, it is faster; image sequences can be acquired rapidly without waiting for a flash to recharge. Finally, less scatter produces images with better contrast; the highly collimated beam and, optionally, a confocal aperture, reduce light scatter from structures elsewhere in the retina. These features combine to make it a very versatile instrument.[73]

The principle of the tomographic SLO

The SLO produces an image by rapid, two dimensional scanning of a laser spot across the retina. Any laser wavelength can be used, but red or infrared light is usually chosen for three dimensional imaging since the longer wavelengths penetrate further. A confocal aperture placed in the optical path in front of the detector allows only light from a given depth range to be collected. A three dimensional volume is formed from a series of two dimensional images at different depths selected by the confocal aperture position.

A commercial product, the Heidelberg retinal tomograph II (HRT II, Heidelberg Engineering; http://www.heidelbergengineering.com), performs confocal tomography using a red (670 nm) diode laser; 32 slices are acquired from different depths, each 384×384 pixels, covering a 15°×15° field of view (corresponding to approximately 4.5×4.5 mm on the retina or 12 μm per pixel).

Two methods have been proposed to measure thickness using the three dimensional dataset. Both are based on analysis of the axial intensity profile of each pixel. Since the eye cannot remain perfectly still during acquisition, the first step is the automatic alignment of the slices to compensate for movement. An axial intensity profile, showing brightness versus depth, can then be generated for each pixel.[74]

The depth at which the peak intensity occurs, assumed to correspond to the vitreous/retinal interface, can be recorded to produce a topographic map. However, the map only provides the anterior retinal surface; thickness measurement requires a credible reference plane. Zambarakji *et al* used a system where the operator selects the location for the reference plane, based on visual inspection of the topographic image.[75] The volume above the reference plane is then calculated for a 2 mm circular region of interest centred on the fovea.

Alternatively, the width of the axial intensity distribution may be analysed, which avoids having to specify a reference plane. Like the RTA analysis, a non-linear curve fitting algorithm can be used to measure the width of the intensity distribution robustly.[76] The profile width may be normalised by the maximum signal intensity at the point to give an ''oedema index''.[77]

The performance of the SLO

Resolution

The SLO has good lateral resolution (approximately 10–20 μm), but much poorer axial resolution. Although Degenring *et al* quote a 60 μm axial resolution,[41] this is unrealistic in practice, and must assume a very small confocal aperture, large pupil size and no optical aberrations. A more realistic figure is 150–300 μm.[74]

Sensitivity

Few studies have evaluated the HRT for detecting macular oedema. Guan *et al*, treating clinical assessment as the gold standard, found the HRT to have a sensitivity and specificity of 92% and 68%, respectively, compared with 57% and 71% for the RTA. The agreement between the HRT and RTA was described as poor, and they concluded that the HRT agreed better with the clinical assessment.[65] Degenring *et al* concluded that OCT3 was better for detecting oedema than the HRT II.[41]

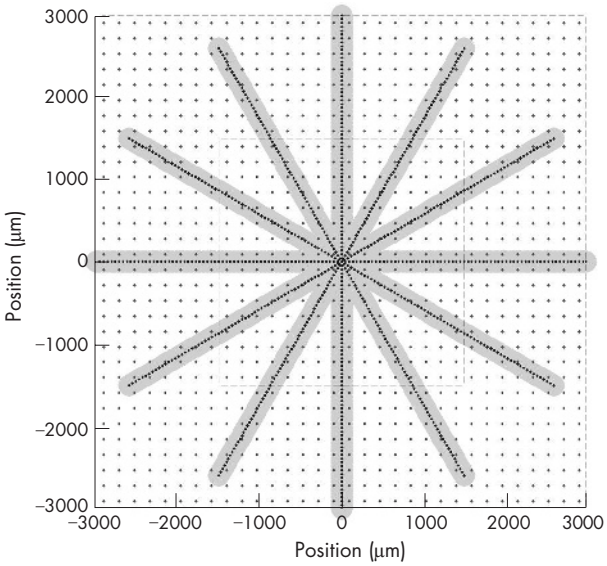

Figure 1 Comparison of 6 mm diameter OCT and RTA 6×6 mm retinal map measurements. The spoke-shaped pattern of dots represents the lines of 128 samples used in the OCT fast retinal map protocol, and the 32×32 rectilinear grid of points represents the RTA samples. The shaded region around the spokes indicates where the OCT sampling resolution is equal to or exceeds that of the RTA.

Repeatability and reproducibility

Zambarakji *et al* found measuring the volume above the topographic reference plane to be only moderately reproducible: in normal subjects the mean intra-session COV was 8%, and the inter-session COV 20%.[75] In diabetic eyes the intra-session COV increased to 18% and the inter-session COV to 30%.[78] Ang *et al* refined the method by allowing the reference plane position to change between scans, and tracing the location of the region of interest and vasculature onto a transparency from the screen.[79] The inter-session COV was reduced to 13% in normal controls and 9% in eyes with macular oedema. Pallikaris *et al* found the oedema index to be a more reproducible measure with a COV of 6% in controls and 10% in eyes with macular oedema.[80]

CONCLUSIONS

The optical techniques have the best resolution and sensitivity, while ultrasound is the method of choice when imaging optically dense media. Although it has been used in a number of research studies,[81–83] magnetic resonance imaging was not included in this review since it currently cannot compete with the other techniques: it is slower than the optical methods, has lower resolution than ultrasound, and is expensive to perform.

The more difficult choice is between the three optical techniques. Each has features that make it the method of choice in particular situations. OCT has the largest user base, the best axial resolution, produces thickness measurements that are independent of refractive error, and can often be used without mydriasis. However, it is relatively slow, which forces a radial, rather than rectilinear, sampling pattern for the thickness map. Even using the OCT3 fast mapping protocol, the thickness map takes six times longer to acquire than with the RTA. Furthermore, the resolution of the OCT map is very poor away from the radial spokes. Figure 1 shows that the resolution of the RTA map is superior to OCT over most of the map area.

However, despite the resolution and speed advantages of the RTA, a number of studies have found OCT to be the more sensitive test for detecting macular oedema,[67] to correlate better with clinical assessment,[44 84] and to have a lower technical failure rate.[63] Three issues may contribute to the lower technical failure rate. Firstly, OCT uses a longer, more penetrating wavelength. Secondly, the RTA requires an 15° angle between the incident and reflected beams, increasing the probability of encountering opacities. Thirdly, OCT measures depth by optical path length rather than reflected intensity.

Studies using the HRT have reported only mediocre reproducibility, but its main drawback is its poor axial resolution. This is a particular problem in cystoid macular oedema, where the resolution is insufficient to resolve the anterior surfaces of the cysts (which are visible on OCT). Consequently, the topographic map follows the posterior surface, showing the cyst as a depression.

Despite some reservations regarding the resolution of the thickness map, OCT currently appears to be the most reliable and sensitive technique for detecting and measuring macular oedema. Ultrasound has a role where optical imaging is not possible.

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